REMARKS

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action mailed November 2, 2005.

Applicants take this opportunity to bring to the Examiner's attention copending application serial number 10/652,686, assigned to Curis, Inc.

Elections/Restrictions

The Examiner has acknowledged Applicants' election, with traverse, of Group I (claims 1-9, 17, 18, and 21-22) in the response filed on September 14, 2005. Applicants acknowledge that the election requirement is now made final. The election specifies selection of colon cancer and an anti-hedgehog antibody in claims 5 and 17, respectively, for search purposes only. The Examiner has considered claims 1-3, 5, 17, 21, and 22.

Information Disclosure Statement

The Examiner states that certain of the US provisional or unpublished patent applications cited by Applicants in the information disclosure statement mailed on Dec. 12, 2002 do not comply with 37 CFR 1.97. Applicants enclose herewith a supplemental information disclosure statement providing the publication numbers of the previously cited provisional and unpublished patent applications originally cited by their U.S. serial number.

Oath/Declaration

The Examiner notes that a signed copy of the declaration was not submitted as of the mailing date of this office action. However an executed declaration was mailed on January 14, 2002, as part of the reply to a notice of missing parts. A copy of the executed declaration is also enclosed herewith.

Claim Objections

Claim 17 is objected to because the claim purportedly encompasses non-elected inventions and non-elected species. Applicants note that the election of species was made for search purposes only. Claims 17 and 18 are withdrawn from consideration. However, upon allowance of a generic claim, Applicants will be entitled to a rejoinder of the withdrawn claims.

Applicants have canceled claim 22, without prejudice, in response to the Examiner's objection on page 4 of the office action.

Claim Rejections – 35 § USC 112, 1st paragraph, enablement

Claims 1-3, 5, 17, 21, and 22 are rejected because the specification allegedly fails to enable one of skill in the art to practice the claimed invention. The Examiner states the aforementioned claims are rejected "because the specification, while being enabling for a method of using a hedgehog antibody 5E1, or cyclopamine, to inhibit unwanted cell proliferation of a pancreatic, bladder, colon, prostate, lung, or colon cancer cell line overexpressing the gli1 or Shh genes, either 1) in vitro or 2) subcutaneously injected in a mammal, does not reasonably provide enablement for other methods of inhibiting unwanted cell proliferation, including other forms of in vivo treatment." (pages 4-5 of the office action). Applicants respectfully traverse this rejection.

The Examiner states that the examples provided, while demonstrating "enablement of subcutaneously implanted cancer cell lines ... do not provide enablement for treatment of 'native' tumors..." (page 6, lines 10-14 of the office action). The Examiner cites art to highlight purported shortcomings of the murine xenograft model, namely (1) differences between the subcutaneous microenvironment and the microenvironment of the colon, (2) potential differences between cell lines and in vivo-derived tumor cells, and (3) possible difficulties due to the pharmacokinetic properties and metabolism of antibodies (pages 6-7 of the office action). Applicants respectfully disagree.

The animal model and cell lines used in the present application constitute an accepted model for predicting the in vivo efficacy of a test agent compared to a control agent or treatment. For example, Takahashi et al. (Gastroenterology 1995 (108): 172-182, enclosed herewith as Exhibit A) used a human colonic cell line in a mouse xenograft model to determine the efficacy of an SF-25

antibody in inhibiting metastasis. The authors submit "there are several limitations inherent in the nude mice xenograft model; nevertheless, this experimental animal model provides a functional system to investigate some of the in vivo antitumor properties of the chimeric SF-25 antibody" (page 181, first column). Further, Kuriyama et al. (enclosed herewith as Exhibit B) subcutaneously inoculated mice with colon adenocarcinoma cell lines and tested various treatments on tumor growth inhibition and animal survival. The authors extrapolate that the results derived from this model system indicate the treatments used "can be successfully employed for the treatment of internal cancers, including CRC [colorectal cancer], as well as superficial cancers" (page 1576, first column of Dig. Dis. Sci. 2000 (45): 1568-1577, and references cited therein).

Moreover, in a review of the literature on human tumor xenografts as predictive preclinical models for anticancer drug activity, Kerbel states "human tumor xenografts—even non metastatic ectopic/subcutaneous 'primary' tumor transplants—can be remarkably predictive of cytotoxic chemotherapeutic drugs that have activity in humans, when the drugs are tested in mice using pharamcokinetically clinically equivalent or 'rational' drug doses" (see abstract and page S135, second column of Cancer Bio. Ther. 2:4 2003: S134-S139, Exhibit C). Therefore, the experimental model used in the present application constitutes a system accepted in the art to be representative and predictive of efficacy in vivo.

Further, the experiments described in the disclosure are intended to be merely illustrative in providing assessments of the relative efficacy of two treatments—a hedgehog antagonist and a control treatment. These two treatments are subject to the same limitations of the model so that the efficacy of the antagonist can be appropriately determined. Accordingly, the relative efficacy of the antagonist versus the control in the model system can be extrapolated to predict the relative in vivo efficacy of the two treatments against a native tumor (see above references). Indeed, Heijstek et al. (page 20) submit that "[t]he accessibility of subcutaneous tumors is a tremendous advantage for monitoring tumor progression and for assessing the effects of therapeutic intervention."

Applicants provide unambiguous teachings of the methods of the disputed claims. Applicants describe the identification of useful hedgehog antibodies (see, for example, page 88), and provide methods for determining *gli-1* expression level (see, for example, page 100 and page 136). Furthermore, Applicants demonstrate the efficacy of an anti-hedgehog antibody in inhibiting

colon tumor growth (see, for example, pages 152-153). Applicants support these teachings with illustrative working examples which are clearly "not intended to limit the scope of the invention" (page 132, lines 7-8). The Examiner states "one of skill in the art would need to engage in undue experimentation in order to determine whether or not the hedgehog antagonist would actually work to treat a tumor in the colon." However, as stated above, the experiments provided in the disclosure represent predictive examples of efficacy and utility in vivo.

Decisions from the Federal Circuit clearly support the conclusion that if an in vitro model correlates with an in vivo activity, then the in vitro model constitutes a working example. See MPEP 2164.02 citing *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985): "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention.... [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)" Further, in *In re Brana* the court states "If applicants were required to wait until an animal naturally developed this specific tumor [lymphocytic tumors] before testing the effectiveness of a compound against the tumor in vivo...there would be no effective way to test compounds in vivo on a large scale." It follows from the reasoning in these cases that evidence obtained using an accepted in vitro animal model like the mouse xenograft model constitutes a working example supporting in vivo efficacy. This evidence supports the enablement of the claimed methods for both in vitro and in vivo use. Reconsideration and withdrawal of this rejection is requested.

The Examiner also rejects the aforementioned claims on the grounds that a *gli* gene as recited in the claims includes the three *gli* genes (*gli1*, *gli2* and *gli3*) but that Applicants have only demonstrated overexpression of *gli1*. The Examiner cites Sanchez et al. to state that the relevant art teaches that *gli2* and *gli3* are not consistently expressed in prostate cancer cells (page 7, item #1 of the office action). Applicants respectfully disagree. Consistent expression of a *gli* gene in cancer samples is not a requirement of the claimed methods because the methods of the current claims

comprise the step of determining *gli* gene expression. This step of determining the expression level of a *gli* gene renders irrelevant the consistency of *gli* gene expression among a given set of samples.

Nevertheless, to expedite prosecution, Applicants have amended the claims to limit more particularly point out the claimed subject matter. Specifically, Applicants have amended the claims to more particularly point out a step of determining expression of *gli-1*. Applicants' amendments are made solely to expedite prosecution and are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

The Examiner also states that "[i]t is not predictable whether or not other antagonists could function to inhibit unwanted cell proliferation" when referring to antagonists other than the 5E1 antibody and cyclopamine used in the illustrative examples. However Applicants explicitly teach methods for identifying and generating efficacious antagonists including small molecules (pages 30-81), *hedgehog* mutants (pages 81-88), antibody antagonists (page 88) and ribozyme and nucleic acid antagonists (pages 89-95). Although screening these agents for antagonistic effects is routine, Applicants describe screening assays to identify *hedgehog* mutants exhibiting antagonistic effects on pages 86-88 and describe the selection of other agents with antagonistic effects on page 96. Moreover, on page 142 Applicants demonstrate that a small molecule antagonist identified through screening (compound A) functions to inhibit unwanted cell proliferation. Applicants also teach screening for antagonistic agents in Example 9 (pages 153-154), where Applicants advise that the assays described in the specification can be used to determine the ability of an agent to inhibit cell growth and proliferation. Applicants have clearly taught the generation and identification of various types of hedgehog antagonists that act to inhibit cell growth, and Applicants have successfully enabled the full scope of the term hedgehog antagonist. Furthermore, as stated above, the assays and examples provided in the specification can be extrapolated to predict the efficacy of the antagonists against tumors.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out the claimed subject matter. Specifically, Applicants have amended the claims to more particularly point out that the antagonists used in the subject methods are hedgehog antibodies. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the

right to prosecute claims of similar or differing scope. In light of Applicants' arguments and amendments, Applicants request reconsideration and withdrawal of the rejection.

In response to the Examiner's rejection of claims 21 and 22 (page 8, item #3) of the office action, Applicants have amended claim 21 to recite a method comprising a determination of *gli-1* gene expression. Support for this amendment is provided in the specification on, for example, page 8 (third paragraph), page 100 (third paragraph), and pages 136 and 144. Additionally, Applicants have canceled claim 22, thereby rendering this rejection moot.

In view of the foregoing remarks and amendments, Applicants contend that the pending claims are enabled throughout their scope. Applicants respectfully request reconsideration and withdrawal of the rejections under 35 § USC 112, first paragraph, enablement.

Claim Rejections – 35 § USC 112, 1st paragraph, written description

Claims 1-3, 5, 17, 21, and 22 are rejected under 35 § USC 112, first paragraph for allegedly failing to comply with the written description requirement. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

The Examiner states "[t]he instant specification fails to describe the entire genus of hedgehog antagonists that will work with the claimed inventions" (page 10, first paragraph). The Examiner further states that "[t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (page 10, third paragraph of the office action).

In Section III Exemplary Compounds and Synthesis Thereof (pages 30-81), Applicants provide structural examples of small molecules that can be used in routine screening assays to identify hedgehog antagonists, and Applicants further provide working examples of small molecule antagonists in Figures 1, 2A, and 2B along with a structural example of a hedgehog agonist (Figure 3). Thus, Applicants have depicted representative examples of small molecule antagonists and

therefore have satisfied the written description requirement for this class of agents. Applicants have also demonstrated that certain of these small molecule antagonists, as well as an anti-hedgehog antibody, can inhibit cell proliferation and reduce tumor cell growth in model systems accepted in the art to be predictive of efficacy in vivo (see above). Applicants have also provided descriptions of other classes of agents (e.g., polypeptide antagonists such as *hedgehog* mutants and antibodies, and nucleic acid antagonists such as antisense, ribozyme, and triplex methods) that can serve as hedgehog antagonists with sufficient specific details to allow an individual skilled in the art to envision such antagonists.

Nevertheless, to expedite prosecution, Applicants have amended the claims to more particularly point out the claimed subject matter. Specifically, Applicants have amended the claims to more particularly point out that the hedgehog antagonists for use in the claimed methods are anti-hedgehog antibodies. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' arguments and amendments, Applicants request reconsideration and withdrawal of this rejection.

Claim Rejections – 35 § USC 112, 2nd paragraph

Claims 1-3, 5, 17, 21, and 22 are rejected as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

The Examiner alleges that the term "effective" is not defined in the disclosure, thus rendering the amount of hedgehog antagonist to be administered indefinite. Likewise, the Examiner asserts that the term "sufficient" in claim 21 is relative and does not definitively limit the amount of antagonist administered. The term "effective" is explicitly defined on page 15 of the specification. In addition, the standard dictionary term for "sufficient" (e.g., of a quantity that can fulfill a need or requirement but without being abundant) when applied restricts the amount of antagonist administered in the method of claim 21. The term sufficient is used in claim 21 with reference to the phrase "to decrease the growth and/or proliferation of the tumor." In light of the dictionary definition of the term and in light of the context in which the term is used in claim 21, Applicants

contend that "sufficient" is not indefinite. One of skill in the art can readily ascertain the metes and bounds of the claimed subject matter.

Claims 2, 3, 5, 17, 21, and 22 are also rejected for depending from the allegedly indefinite claims 1 and 21. For the reasons detailed above, Applicants contend that the terms "effective" and "sufficient" do not undermine the clarity of the claims. This reasoning is equally applicable to the foregoing dependent claims.

Additionally, the Examiner rejected the claims as "being incomplete for omitting essential steps." The allegedly omitted essential steps are "measuring *gli* gene expression in 'reference' cells (e.g., non-tumor cells) and comparing the *gli* gene expression in order to determine if the test cells (e.g., potential tumor cells) have *gli* gene overexpression" (page 12 of the office action). However the current claims recite "determining whether cells overexpress a *gli* gene." This determination includes the steps delineated by the Examiner, as well as a measurement of *gli* gene expression in the 'test' cells (see page 19, fourth paragraph of the specification). Determining overexpression (as defined on page 19) requires measuring *gli* expression in test cells and comparing this measurement against reference cells. Given that the recited step of "determining whether cells overexpress a gli-1 gene" encompasses taking measurements in a test cell and comparing the measurements against some control, Applicants contend that the claim is complete and does not lack any essential steps.

Applicants contend that the claims are clear and that one of skill in the art can readily ascertain the metes and bounds of the claimed subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 § USC 102(a)

Claims 1-3 and 17 are rejected as allegedly anticipated by Taipale et al. Taipale et al. use murine cells to elucidate the mechanism of action of cyclopamine and its derivatives on the hedgehog pathway. The Examiner states that "Taipale teaches that murine fibroblasts lacking patched overexpress the Gli gene" and that "Taipale teaches a method of inhibiting unwanted cell proliferation that clearly anticipates claims 1-3 and 17" (page 13 of the office action). Applicants respectfully traverse this rejection.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). Taipale et al. fail to anticipate the present invention as set forth in the present claims.

Nevertheless to expedite prosecution, Applicants have amended the claims as detailed above with respect to Applicants' remarks to the rejection under 35 U.S.C. 112, first paragraph. Specifically, Applicants have amended the claims to more particularly point out that the hedgehog antagonist for use in the claimed methods is an anti-hedgehog antibody. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

In contrast to the presently claimed methods, Taipale et al. use small molecules—cyclopamine and its derivatives—to treat murine cells that are deficient in *patched*. Furthermore, the presently claimed methods are used to treat cells specifically determined to overexpress a gli-1 gene. Taipale et al. fail to teach or suggest either of these elements of the claimed invention. Although Applicants contend that Taipale et al. failed to satisfy the requirements for anticipating the claimed invention prior to Applicants' amendments, Applicants' amendments further distinguish the claimed methods from the teachings in Taipale et al. Given that Taipale et al. fail to meet each and every limitation of the claimed invention, Taipale et al. fail to anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim Rejections – 35 § USC 102(e)

Claims 1-3 and 17 are rejected as allegedly anticipated by Baxter et al. (U.S. patent No. 6,545,005). Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

Baxter et al. teach small molecule hedgehog signaling antagonists. Baxter et al. also teach that the antagonists can be used to "inhibit aberrant growth states resulting from activation of the hedgehog signaling pathway..." (column 6, lines 6-7), which include "tumors resulting from gli-1 amplification" (column 45, line 12). However Baxter et al. fail to teach or suggest a method

whereby *gli* overexpression is used as an indicator of hedgehog pathway activation and whereby *gli* overexpression is used as a marker to select cells and/or tumors that are appropriate for hedgehog antagonist therapy. Further, the teachings of Baxter et al. are limited to the use of specific small molecule antagonists. Given that Baxter et al. fail to teach a step of determining gli expression, Baxter et al. fail to satisfy the criteria necessary for undermining the patentability of the claimed invention

Nevertheless to expedite prosecution, Applicants have amended the claims as detailed above with respect to Applicants' remarks to the rejection under 35 U.S.C. 112, first paragraph. Although Applicants' amendments are not in acquiescence to this rejection, Applicants' amendments further distinguish the presently claimed invention from the teachings of the prior art. Given that Baxter et al. neither teach nor suggest the claimed methods of the present invention, Baxter et al. fail to anticipate the claimed invention. Reconsideration and withdrawal of this rejection is requested.

Claims 1-3 are also rejected as allegedly anticipated by Scott et al. (U.S. Patent No. 6,429,354). Scott et al. teach methods for isolating *patched* (*ptc*) genes and determining whether or not a cancer cell has a mutation in *ptc*. The Examiner concludes that because Scott et al. show that both *ptc* and *gli* genes are transcribed in brain tumors but not in surrounding tissues and teach that *gli* expression is partly regulated by patched protein, determining whether the cells have a mutation in *patched* gene inherently determines whether the cells overexpress a *gli* gene (page 14, fourth paragraph of the office action). Applicants respectfully disagree. *Gli* expression is only partly determined by patched protein; other factors, such as Fused, Smoothened, and other proteins, also regulate *gli* gene expression and may therefore affect the ultimate level of *gli* gene expression in a given cell or tumor. For example, Levanat et al. (2004 Ann. N.Y. Acad. Sci. 1030: 134-143, article attached as Exhibit D) examined mutations and polymorphisms in *patched* in ovarian fibroma and dermoid samples and correlated this mutational information with expression of shh, smo, and gli. Levanat et al. showed that most samples in which *ptch* was mutated did not show upregulation of *gli1*; in describing fibromas with LOH in the PTCH locus (pages 138-140), the authors state "the levels of SMO expression were frequently increased..., suggesting that the pathway was activated, although GLI expression was increased only in one case....Similarly, in those dermoid samples in

which PTCH was altered (as indicated by LOH in 9q22.3 locus) and the increased expression of SMO was observed, this was not accompanied by higher levels of GLI1...." (page 140).

Additionally, Scott et al. fail to teach methods wherein tumors or cells are selectively chosen for hedgehog antagonist therapy based on *ptc* (or more directly *gli*) expression levels. Accordingly, given that Scott et al. fail to teach each and every limitation of the claimed invention, Scott et al. fail to anticipate the claimed invention.

Given that neither Baxter et al. nor Scott et al. teach each and every limitation of the claimed invention, the cited references fail to anticipate the claimed subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 § USC 103

Claim 5 is rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Scott et al. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

As outlined above, Scott et al. fails to satisfy the criteria necessary to anticipate the claimed invention. Moreover, Scott et al. fail to recognize the connection between Gli and hedgehog activity, much less suggest a method for inhibiting cell proliferation by detecting gli overexpression and contacting a cell with an anti-hedgehog antibody. The Examiner has not provided any references or other teachings that allegedly overcome the deficiencies of Scott et al. Given that Scott et al. does not suggest or infer the claimed invention, it does not render obvious the claimed invention.

Applicants respectfully submit that none of the cited references teach or suggest each and every limitation of the claimed invention. Thus, the cited references fail to anticipate or render obvious the claimed subject matter. For the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejections.

Double patenting

Claims 1-3, 5, 17, 21, and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-3, 5, 17, 21, and 22 of

copending application 10/652298. As this is a provisional rejection, Applicants respectfully traverse this rejection and request that this rejection be held in abeyance until finding of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945** under order number CIBT-P01-104.

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Respectfully submitted,

By _____

Melissa S. Rones
Reg. No. 54,408
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant